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Recipient Outcomes From Nondirected Live Kidney Donors: A UK-based Cohort Study

Jay Nath, PhD,¹ Kamlesh Patel, MBChB,^{1,2} Melanie Field, MD,¹ James Hodson, BSc,³ Adnan Sharif, MD,⁴ Nicholas G. Inston, PhD,¹ and Andrew R. Ready, MD¹

Background. Increasing numbers of patients with end-stage renal failure are receiving kidneys from nondirected kidney donors (NKDs), also known as altruistic donors. Transplant outcomes for recipients of such kidneys are largely inferred from studies on specified kidney donors (SKDs), which may be inaccurate due to differences in donor, recipient and transplant specific factors. We report the outcomes for recipients of NKD in the United Kingdom. **Methods.** Outcomes for 6861 patients receiving a living donor kidney transplant between January 2007 and December 2014 were analyzed using both the National Health Service Blood and Transplant and the UK Renal Registry datasets. Graft and patient outcomes were compared for patients receiving NKD and SKD organs using univariable and multivariable analyses. **Results.** There was significant discordance between the NKD and SKD donors and recipients. These included increased donor age (median, 58 years vs 47 years; $P < 0.001$) and higher rates of hemodialysis and previous transplants in the NKD group (both $P < 0.001$). Despite such markers of increased risk among both donors and recipients of NKD kidneys, there was no difference in graft survival on univariable (hazard ratio, 1.20; 95% confidence interval, 0.77-1.86; $P = 0.419$) or multivariable analysis (hazard ratio, 1.13; 95% confidence interval, 0.65-1.95; $P = 0.665$). **Conclusions.** Despite some markers of transplant complexity, nondirected kidney donor organs are an excellent source of organs for transplantation.

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The Human Tissue Act 2004¹ included regulatory oversight for living kidney donation, and thus, nondirected kidney donation was allowed for the first time when it came into force. Nondirected kidney donor (NKD) organs, also known as

altruistic, good Samaritan, anonymous, or unspecified, donor kidneys, are donated to a nondirected recipient without an emotional link.² The number of nondirected kidney donors has increased dramatically following this, with a near fourfold increase in the United Kingdom between 2010 and 2014 (Figure 1), similar to trends observed in the United States.³ Nondirected kidney donor organs are now an important source of donor kidneys and recent data demonstrate they now constitute over 6% all live donor transplants performed in the United Kingdom⁴ and 3% in the United States.³

Allocation of NKD organs has been a source of debate for both ethicists and clinicians alike. Although practices vary between institutions, these organs are normally either allocated to patients on the nationwide deceased-donor waiting list or used to trigger a transplantation chain. Although various models have been proposed to optimize such chain usage,⁵⁻⁹ the net result is that availability of a single NKD organ facilitates 2 or more transplants.^{10,11}

A recent study of donors of NKD organs found that they were older, with a greater proportion of retirees, compared with specified kidney donor (SKD) counterparts.¹² This may have negative consequences, given the correlation between increasing donor age and less favorable transplant outcomes.¹³⁻¹⁵ In addition to donor differences, recipients of NKD organs also differ from the SKD cohort. The majority of NKD organs are allocated to the deceased-donor waiting list, where recipients are generally more medically complex

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¹ Department of Renal Surgery, University Hospital Birmingham, Birmingham, United Kingdom.

² Department of Nephrology, University Hospital Birmingham, Birmingham, United Kingdom.

³ Department of Biostatistics, University Hospital Birmingham, Birmingham, United Kingdom.

⁴ School of Medical and Dental Science, University of Birmingham, United Kingdom.

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Correspondence: Jay Nath, PhD, Department of Renal Surgery, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, United Kingdom. (jay.nath@nhs.net).

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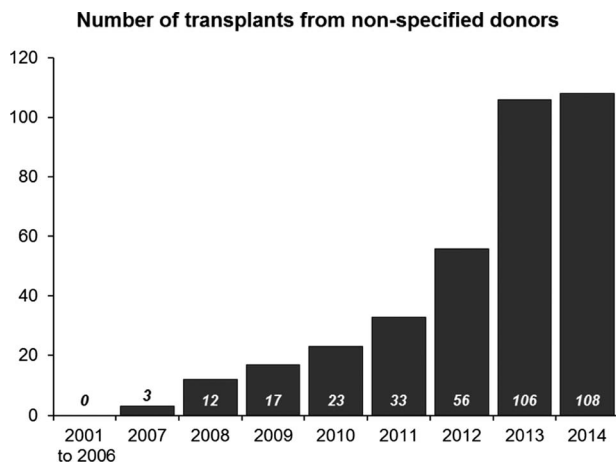


FIGURE 1. Numbers of nondirected kidney donors per year.

than the standard live donor recipient.¹⁶ Although the prognostic significance of close HLA compatibility is less important for graft longevity than it once was, SKD kidney are often from genetically related individuals (eg, siblings / parents) which are known to have a greater degree of genetic match, compared to genetically unrelated kidneys.¹⁷ Finally, the donor nephrectomy and organ implant for NKD operations are often performed at the transplant centers closest to each donor/recipient, resulting in split-site procedures involving 2 separate medical teams, organ transport, and a resultant increase in cold ischemic time (CIT).

Yet despite the differences between SKD and NKD transplants and the increasing importance of NKD transplants, the outcomes for the recipients of these kidneys have not been assessed in a large data set, although reports from small series are encouraging.^{18–22} We hypothesize that NKD transplants have excellent outcomes despite the differences in donor-, recipient-, and transplant-specific factors and aim to test this hypothesis using the United Kingdom national data set.

MATERIALS AND METHODS

Study Design

Retrospective cohort registry study of patients receiving a living donor kidney transplant. The association between donor type (NKD vs SKD) and outcome was assessed. Primary outcome measures were allograft survival (death censored) and patient survival. Secondary outcome measures included creatinine values (at 1 year) and delayed graft function (DGF), defined as the need for dialysis in the first week after transplantation.

Study Population

Adult patients (older than 18 years) receiving a single organ living donor kidney transplant between January 2007 and December 2014 in the United Kingdom were included. Kidney transplant centers within the United Kingdom are obliged to submit demographic and clinical data to both NHS Blood and Transplant (NHSBT) and Renal Registry professional bodies for each transplant performed. The 2 bodies collect different patient specific and outcome variables and therefore amalgamation of the 2 data sets was performed in an attempt to maximize the variables included. This study was approved by the 2 database review boards

above, but did not require separate ethical board approval, due to the nature of the study performed.

Statistical Methods

Initially, a range of factors were compared between the SKD and NKD cohorts. Categorical variables were analyzed using χ^2 tests. Continuous variables were assessed for normality before the analysis, with independent samples *t* tests used where this assumption was met, and Mann-Whitney tests used for nonnormal or ordinal data.

Survival outcomes in the 2 groups were assessed using Kaplan-Meier curves, with hazard ratios (HRs) and *P* values from univariable Cox regression models. These were followed by multivariable Cox regression analyses, in order to compare the outcomes of the 2 groups, after accounting for potentially confounding factors. The donor type was entered into the model, alongside all of the potentially confounding factors for which data were available. Continuous variables were converted into ordinal categories, to improve model fit, with ethnicity and graft number dichotomized, to give sufficient within-category sample sizes to produce reliable HRs. Because of the amount of missing data for the wait time and sensitization, a sensitivity analysis was performed by generating separate models with and without considering these factors. These gave consistent results; hence, the latter is quoted throughout to maximize the sample sizes considered.

A similar approach was employed for the analysis of 1 year creatinine and DGF. The former was \log_{10} -transformed, before analysis, in order to normalize the distribution, before being compared between the groups using an independent samples *t* test and multivariable general linear model. The coefficients from the multivariable model were then antilogged, and converted into percentage differences between groups for ease of interpretation. Rates of DGF were compared between the groups using a χ^2 test, with multivariable analysis by binary logistic regression.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY). Cases with missing data were excluded on a per-analysis basis, and *P* less than 0.05 was deemed to be indicative of statistical significance throughout.

RESULTS

Patient Demographics

Data were available for 6861 transplants between January 2007 and December 2014, of which 358 (5.2%) were from nondirected donors. The number of NKDs increased significantly over the period of the study (Kendall's Tau: $P < 0.001$, Figure 1). The first recorded NKD transplants ($n = 3$) occurred in 2007, accounting for less than 0.5% of the total living transplants that year, increasing to 12% of living transplants by 2014 ($n = 108$).

Comparisons of donor and recipient factors in NKD and SKD groups are reported in Table 1A. Nondirected donors were found to be significantly older ($P < 0.001$), more likely to be male ($P = 0.010$) and of white ethnicity ($P < 0.001$) and to have significantly lower BMI ($P < 0.001$) than specified donors.

There were also differences between the recipients of NKD organs compared to SKD counterparts. Recipients of NKD organs were significantly older, and less likely to be male and of white ethnicity (all $P < 0.001$). The NKD recipients

TABLE 1A.
Association between kidney type and patient demographics

	Valid, n	Donor type		P
		Specified	Nondirected	
Donor factors				
Age (median + IQR)	6861	47 (39-56)	58 (48-65)	<0.001
Sex (male)	6860	2978 (45.8%)	189 (52.8%)	0.010
BMI, mean (SD) ^a	6541	26.6 ± 4.0	25.4 ± 3.3	<0.001
Ethnicity	6855			<0.001
White		5581 (85.9%)	352 (98.3%)	
Asian		525 (8.1%)	5 (1.4%)	
Black		269 (4.1%)	1 (0.3%)	
Other		122 (1.9%)	0 (0.0%)	
Blood group	6846			<0.001
A		1968 (30.3%)	183 (51.1%)	
B		480 (7.4%)	32 (8.9%)	
O		4040 (62.3%)	143 (39.9%)	
Recipient factors				
Age (median + IQR)	6861	45 (34-56)	49 (41-59)	<0.001
Sex (male)	6853	3925 (60.4%)	189 (52.8%)	0.005
Ethnicity	6781			<0.001
White		5476 (85.2%)	278 (78.1%)	
Asian		555 (8.6%)	51 (14.3%)	
Black		282 (4.4%)	23 (6.5%)	
Other		112 (1.7%)	4 (1.1%)	
Diabetes	6861	389 (6.0%)	26 (7.3%)	0.306
Dialysis at transplant	6296			<0.001
Hemodialysis		2940 (49.3%)	235 (71.2%)	
Peritoneal dialysis		1183 (19.8%)	74 (22.4%)	
Not on dialysis		1843 (30.9%)	21 (6.4%)	
Graft number	6861			<0.001
1		5639 (86.7%)	271 (75.7%)	
2		723 (11.1%)	68 (19.0%)	
3+		141 (2.2%)	19 (5.3%)	
CMV positive	6491	2851 (46.3%)	180 (53.4%)	0.012
Blood group	6861			<0.001
A		2836 (43.6%)	163 (45.5%)	
AB		213 (3.3%)	25 (7.0%)	
B		765 (11.8%)	46 (12.8%)	
O		2689 (41.4%)	124 (34.6%)	

P values from Mann-Whitney for continuous variables, and χ^2 tests for categorical variables, unless stated otherwise.

^a P value from independent samples t test.

IQR, interquartile range.

were also significantly more likely to have previously received a renal transplant, with higher rates of pretransplant hemodialysis and lower rates of preemptive transplantation also noted (all $P < 0.001$).

Of the matching and surgical factors considered (Table 1B), NKD organs had multiple markers of transplant complexity with significantly longer CIT, waiting list duration, and degree of sensitization (all $P < 0.001$). There were fewer HLA mismatches in the NKD group compared with SKD organs ($P < 0.001$).

Univariable Analyses of Survival Outcomes

Outcome measures for SKD and NKD groups were compared using univariable analyses (Table 2). These found no significant difference in rates of allograft survival (death

censored) between the NKD and SKD groups (HR, 1.20; 95% confidence interval [CI], 0.77-1.86; $P = 0.419$; Figure 2a). However, patient survival was inferior in the NKD group, relative to SKD, with 1- and 3-year survival rates of 96.9% versus 98.9% and 92.8% versus 97.2%, respectively (HR, 2.60; 95% CI, 1.66-4.07; $P < 0.001$; Figure 2B).

Multivariable Analysis of Survival Outcomes

Multivariable Cox regression models were then produced to account for the effects of potentially confounding factors (Table 3). Patient survival was found to be significantly shorter in older recipients, those with diabetes or CMV, and patients on hemodialysis at the time of transplant. In addition, recipients of organs from older donors and those with HLA incompatibility also had significantly shorter survival. After accounting for these factors, no significant difference in patient survival between NKD and SKD organs was detected (HR, 1.68; 95% CI, 0.90-3.16; $P = 0.104$).

Multivariable analysis of death-censored allograft survival also found hemodialysis at transplant, increasing donor age and HLA incompatibility to be significantly predictive of poorer prognosis. In addition, younger recipients, and those who had received previous transplants also had significantly shorter death-censored allograft survival. After accounting for these factors, no significant difference between NKD and SKD organs was detected (HR, 1.13; 95% CI, 0.65-1.95; $P = 0.665$).

Other Outcomes

Creatinine levels at 1 year were available in 5259 patients. Geometric mean levels were similar in the 2 patient groups

TABLE 1B.
Association between kidney type and matching/transplant factors

	Valid, n	Donor type		P
		Specified	Nondirected	
CIT: median (IQR), min	6239	180 (120-231)	330 (242-408)	<0.001
Wait time: median (IQR)	5036	261 (105-562)	1141 (597-1730)	<0.001
Sensitization	4721			<0.001
0		2578 (59.1%)	173 (48.5%)	
1-20		255 (5.8%)	23 (6.4%)	
21-80		932 (21.4%)	85 (23.8%)	
81-100		599 (13.7%)	76 (21.3%)	
Year of transplant	6861			<0.001
2007-2008		1530 (23.5%)	15 (4.2%)	
2009-2010		1676 (25.8%)	40 (11.2%)	
2011-2012		1641 (25.2%)	89 (24.9%)	
2013-2014		1656 (25.5%)	214 (59.8%)	
HLA mismatch group	6844			<0.001
1		669 (10.3%)	74 (20.7%)	
2		855 (13.2%)	138 (38.5%)	
3		3005 (46.3%)	121 (33.8%)	
4		1957 (30.2%)	25 (7.0%)	
AITX type ^a	6861			0.350
Not present		6123 (94.2%)	342 (95.5%)	
HLAi		380 (5.8%)	16 (4.5%)	

P values from Mann-Whitney tests on noncategorized data, unless stated otherwise.

^a P value from χ^2 test.

HLAi, incompatible.

TABLE 2.
Summary of graft survival analyses

Outcome	Kaplan-Meier estimated survival at:			Cox regression analysis			
	1 y	2 y	3 y	Univariable		Multivariable ^a	
				HR (95% CI)	P	HR (95% CI)	P
Patient survival							
Specified	98.9%	98.1%	97.2%	—	—	—	—
Nondirected	96.9%	95.5%	92.8%	2.60 (1.66-4.07)	<0.001	1.68 (0.90-3.16)	0.104
Allograft survival (death censored)							
Specified	97.0%	95.7%	94.2%	—	—	—	—
Nondirected	95.4%	93.6%	92.8%	1.20 (0.77-1.86)	0.419	1.13 (0.65-1.95)	0.665

Univariable survival analyses are based on the 6813 patients with survival data reported.

^a Full models are reported in Table 3.

($P = 0.885$), at 120.1 $\mu\text{mol/L}$ versus 120.4 $\mu\text{mol/L}$ in transplants from SKD versus NKD (Table 4). This difference remained nonsignificant after accounting for potentially confounding factors on multivariable analysis ($P = 0.294$).

The DGF rates were found to be significantly higher in nondirected donors in univariable analysis (6.3% vs 3.9%; $P = 0.037$). After accounting for potentially confounding factors in a multivariable analysis, this difference became nonsignificant ($P = 0.370$), with an odds ratio of 0.92 (95% CI, 0.50-1.67; $P = 0.777$) for nondirected versus specified donor kidneys.

DISCUSSION

This is the largest published study to report recipient outcomes for NKD organs, using a national data set with a high proportion of such donors. We found, as anticipated, that NKD kidney have excellent outcomes and, after adjusting for significant confounding donor and recipient factors, these were comparable to SKD organs.

This study serves to highlight that there are a multitude of differences between the NKD and SKD transplants with regard to donor-, recipient-, and transplant-specific factors, which must be considered when counseling a potential NKD recipient. First, donors of NKD organs are on average more than a decade older than SKD counterparts, with 40% of NKD donors older than 60 years. Such age equivalent kidneys are classified as extended criteria in the cadaveric setting, with associated inferior outcomes (other qualifiers are donor aged 50 to 59 years with at least 2 of the other 3 conditions (cerebrovascular cause of death, renal insufficiency [serum creatinine, $>132 \mu\text{mol/L}$], and hypertension).^{23,24} Second, there are inherent differences in recipients of NKD kidneys, compared with SKD counterparts, with higher levels of sensitization, longer waiting list times and a higher proportion on hemodialysis before transplantation (Table 1B). Thirdly, NKD organs transplanted in the United Kingdom are normally performed across different donor and recipient sites. This adds a degree of logistical complexity to NKD transplantation, and inevitably, the CIT is prolonged. Interestingly, the degree of HLA mismatch is actually greater for SKD organs, which is perhaps surprising given that NKD organs are always from unrelated individuals. However, this is likely to reflect the priority given to matching recipients of such organs for patients on the cadaveric kidney waiting list.

However, despite these markers of transplant complexity associated with NKD organs in the United Kingdom, the outcomes for such kidneys are excellent. Indeed, even before adjustment for these confounding factors, there was no significant difference in graft survival or 1 year creatinine values between NKD and SKD kidneys. We hope these results

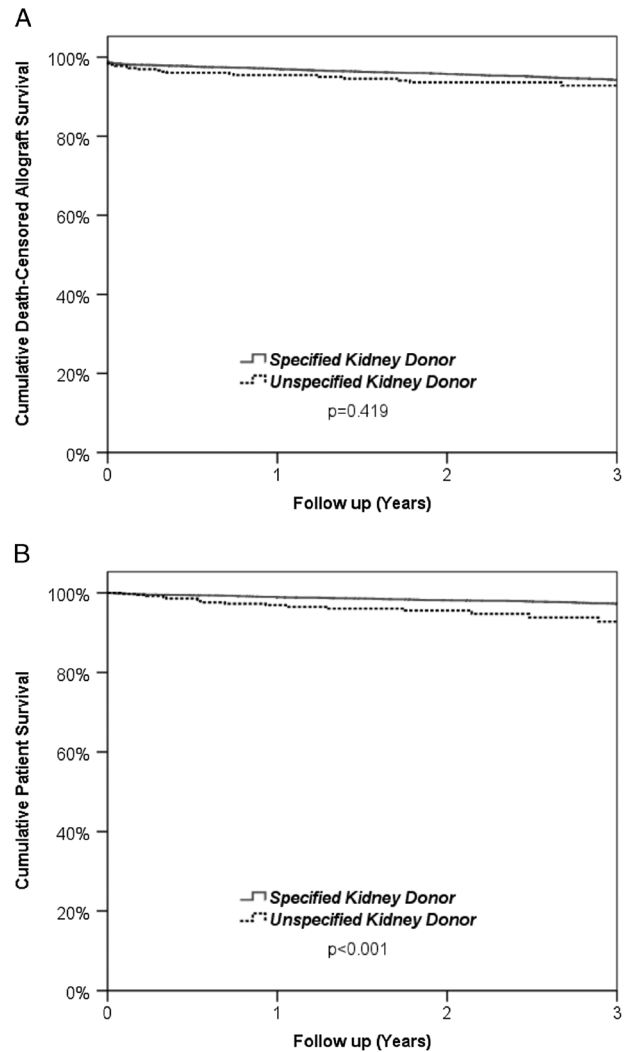


FIGURE 2. A, Kaplan-Meier curve of death-censored allograft survival. B, Kaplan-Meier curve of patient survival.

TABLE 3.**Multivariable analysis of survival outcomes**

	Patient survival		Allograft survival (death-censored)	
	HR (95% CI)	P	HR (95% CI)	P
Donor type (nondirected)	1.68 (0.90-3.16)	0.104	1.13 (0.65-1.95)	0.665
Recipient age, y		<0.001		<0.001
< 40	—	—	—	—
40-49	2.08 (1.22-3.53)	0.007	0.65 (0.49-0.85)	0.002
50-59	3.24 (1.92-5.48)	<0.001	0.54 (0.39-0.74)	<0.001
60+	7.71 (4.70-12.62)	<0.001	0.62 (0.44-0.87)	0.006
Recipient sex (Male)	1.08 (0.80-1.47)	0.599	0.86 (0.70-1.07)	0.178
Recipient ethnicity (nonwhite)	0.56 (0.25-1.23)	0.148	1.02 (0.60-1.74)	0.930
Recipient diabetes (yes)	2.43 (1.62-3.66)	<0.001	0.83 (0.50-1.38)	0.473
Dialysis at transplant		<0.001		0.010
Hemodialysis	—	—	—	—
Peritoneal dialysis	0.55 (0.36-0.82)	0.003	0.81 (0.62-1.07)	0.139
Not on dialysis	0.53 (0.37-0.76)	0.001	0.66 (0.50-0.87)	0.003
Previous grafts (yes)	1.37 (0.88-2.15)	0.164	1.57 (1.18-2.10)	0.002
Recipient CMV (positive)	1.37 (1.03-1.84)	0.033	0.99 (0.80-1.23)	0.926
Recipient blood group		0.371		0.691
A	—	—	—	—
AB	0.30 (0.07-1.25)	0.097	0.73 (0.38-1.42)	0.352
B	0.76 (0.36-1.62)	0.478	0.89 (0.51-1.55)	0.687
O	1.01 (0.67-1.53)	0.967	1.08 (0.79-1.49)	0.618
Donor age, y		0.002		0.016
< 40	—	—	—	—
40-49	1.95 (1.26-3.02)	0.003	1.40 (1.05-1.86)	0.021
50-59	1.24 (0.76-2.01)	0.383	1.07 (0.79-1.46)	0.662
60+	2.08 (1.31-3.33)	0.002	1.55 (1.12-2.17)	0.009
Donor sex (male)	0.90 (0.67-1.21)	0.495	0.89 (0.72-1.10)	0.285
Donor BMI		0.776		0.317
25	—	—	—	—
25-29	1.13 (0.82-1.55)	0.464	1.13 (0.89-1.44)	0.322
30-34	1.14 (0.76-1.71)	0.539	1.32 (0.98-1.77)	0.069
35+	0.67 (0.16-2.74)	0.574	1.32 (0.66-2.62)	0.434
Donor ethnicity (nonwhite)	2.05 (0.91-4.63)	0.082	1.52 (0.88-2.64)	0.137
Donor blood group		0.809		0.604
A	—	—	—	—
B	1.08 (0.41-2.86)	0.875	0.82 (0.42-1.60)	0.565
O	0.90 (0.59-1.37)	0.608	0.85 (0.61-1.18)	0.324
Transplant year		0.514		0.127
2007-2008	—	—	—	—
2009-2010	1.01 (0.71-1.42)	0.964	0.76 (0.58-0.99)	0.042
2011-2012	0.76 (0.48-1.20)	0.236	0.73 (0.54-1.01)	0.054
2013-2014	0.72 (0.37-1.39)	0.332	0.80 (0.54-1.19)	0.278
HLA mismatch group		0.894		0.175
1	—	—	—	—
2	0.96 (0.54-1.71)	0.890	1.32 (0.84-2.07)	0.227
3	0.86 (0.52-1.42)	0.552	1.50 (1.01-2.23)	0.044
4	0.95 (0.56-1.59)	0.835	1.26 (0.82-1.94)	0.283
AITX type (HLAi)	2.08 (1.28-3.39)	0.003	1.72 (1.21-2.44)	0.002
CiT, min		0.378		0.156
< 120	—	—	—	—
120-179	1.04 (0.68-1.57)	0.868	1.26 (0.93-1.69)	0.132
180-239	1.31 (0.89-1.93)	0.165	1.11 (0.83-1.49)	0.493
240+	1.33 (0.87-2.04)	0.192	1.41 (1.02-1.93)	0.035

Results are from multivariable Cox regression models, based on N = 5213, after excluding cases with missing data. Wait time and sensitization were not considered for inclusion in the final models, due to excessive missing data.

TABLE 4.
Summary of other outcomes

Outcomes	Statistic	Difference between groups			
		Univariable		Multivariable	
		Statistic	P	Statistic	P
1 y Creatinine ^a					
Specified	120.1 (119.1-121.1)	—	—	—	—
Nondirected	120.4 (116.2-124.8)	+0.3% (−3.2%, +3.6%)	0.885	−2.2% (−6.1%, 1.9%)	0.294
DGF ^b					
Specified	235/5991 (3.9%)	—	—	—	—
Nondirected	20/318 (6.3%)	1.64 (1.03-2.63)	0.037	0.92 (0.50-1.67)	0.777

^a Data are reported as a geometric mean, or the percentage difference between groups, with 95% CIs. Univariable analysis is from a *t* test based on *n* = 5259, and multivariable analysis is from a general linear model, including all factors from Tables 1A and 1B except for wait time and sensitization, based on *n* = 4202. Both analyses used log₁₀-transformed data, to normalize the distribution of the creatinine measurements.

^b Data are reported as *n*/*N* (%) or as odds ratio (95% CI). Univariable analysis is from a χ^2 test with *N* = 6309, and multivariable analysis used a binary logistic regression model, including all factors from Tables 1A and 1B except for wait time and sensitization, based on *N* = 4874.

provide reassurance to the transplant community and to future potential nondirected kidney donors.

Although in general, kidney donors have reported good health related quality of life following donation,²⁵ there are risks inherent to this operation. Such risks highlight the need for informed consent for living donors and include a small increase in risk of developing to end-stage renal disease, gestational hypertension, and preeclampsia, as well as possible financial loss.^{26,27}

Given the excellent outcomes for NKD kidneys demonstrated, efforts should focus on how best to use such organs. From an organ utilization perspective, the use of NKD organs to initiate transplant chains would seem ideal, with multiple recipients benefitting from a single donated organ. Not only does this increase the beneficiaries of transplantation, it also facilitates the transplantation of patients who would otherwise have been difficult to find an immunologically compatible organ. This could result in a decrease in need for blood group/HLA incompatible transplantation with its associated morbidity and financial costs.²⁸ Given that the use of NKD kidneys to trigger donor chains would appear to satisfy all ethical standpoints, it would seem reasonable to prioritize NKD organs for these purposes.

Although the first report of NKD transplantation was over 4 years ago,²⁹ the practice has only recently become commonplace, with the vast majority of NKD transplants in the United Kingdom performed after 2010. As a result, long term outcome data is not available in this cohort and is a weakness of this study. Although NKD is relatively commonplace in the United Kingdom, compared with many countries, the absolute number of NKD transplant is still relatively small and therefore this study may lack power to detect subtle outcome differences between NKD and SKD cohorts. Although we considered a wide range of factors in this dual data set analysis, this was not exhaustive as some variables, such as recipient BMI, smoking status and surgical technique of donor nephrectomy were not available.

Nevertheless, in this national cohort study, we detail the excellent outcomes for NKD kidneys in the United Kingdom. These results are reassuring, given that they are contributing an increasingly significant portion of live donor transplants performed.

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